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POLYLACTIDE-DRUG MIXTURES

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ABSTRACT OF THE DISCLOSURE

Described and claimed are formulations of polylactide and drug to be introduced into the body which provide a slow sustained release of the drug over a controlled period of time. The polylactide is biodegradable in the body into normal or essentially normal metabolic products that have no deleterious or untoward effect on the body.

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of our earlier application Ser. No. 868,899, filed Oct. 23, 1969, now abandoned.

BACKGROUND OF THE INVENTION

Field of the invention

This invention relates to novel polymer-drug formulations and to their use in bringing about desired biological effects in living organisms, particularly in human beings and warm-blooded animals such as domestic animals and pets.

Description of prior art

There are a number of publications that disclose combinations of polymers and drugs designed to give sustained or delayed release of the drugs in the alimentary tract. For example U.S. Pat. 3,247,066 discloses controlled drug release compositions in which a core comprises a mixture of a drug and a water-swellable colloid which core is coated with a water permeable polymer. When taken by mouth, water in the body fluids permeates the outer coating and causes the contained colloid to swell. The swelling eventually distends and breaks the outer coating thus releasing the drug in its entirety.

U.S. Pat. 3,458,622 discloses oral drug tablets in which the drug is released at a controlled rate up to about 8 hours after ingestion. The material which controls the release rate is a blend of a polymeric vinyl pyrrolidone with a carboxy vinyl hydrophylic polymer.

R. K. Kulkarni et al., Tech. Rept. 6608, U.S. Army Medical Biomechanical Research Laboratory, Walter Reed Army Medical Center, Washington, D.C., April 1966, report histological studies show poly-DL-lactide and poly-L-lactide are nontoxic, non-tissue reactive materials which are biodegradable. However, no concept is present of combining such material with a drug to produce a controlled release drug composition when introduced under the skin of a warm-blooded animal.

Description of the invention

The formulations of this invention are absorbable, nonirritating pharmaceutical compositions consisting of one or more drugs intimately mixed with or coated by a synthetic polylactide designed to release effective amounts of a drug over a predetermined period of time. The invention is of particular value for drugs that require prolonged administration or slow sustained release, for example certain fertility-control drugs or hormones used for hormone-replacement therapy. The polylactide may be considered as a carrier or matrix for the drug and in this document

the term "polylactide" includes both its generic meaning as a polyester derived from an α-hydroxycarboxylic acid and its specific meaning for the polymer derived from lactic acid (α-hydroxypropionic acid). The particular meaning in any given case will be apparent to one skilled in the art.

The novel formulations permit prolonged release of drugs for a controlled period of time from the sites of parenteral administration and minimize the frequency and thus the discomfort and inconvenience associated with conventional injection formulations. Unlike conventional depot injections, the formulations of this invention undergo biodegradation in the body into normal or essentially normal metabolic products, are nonreactive toward body tissue, and can be designed, by controlling molecular weight and composition, to undergo hydrolysis and to release drug from the depot at a desired rate.

The drug

The term "drug" is intended in its broadest sense as defined in the Federal Food Drug and Cosmetic Act Section 201(2)g:

(1) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement of any of them; and

(2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

(4) articles intended for use as a component of any article specified in clauses 1, 2 or 3; but does not include devices or their components, parts, or accessories.

Classes of drug which may be specifically mentioned include agents affecting the central nervous system, e.g. narcotics, such as, for example, morphine; narcotic antagonists, such as naloxone; antipsychotic agents, such as chlorpromazine and molindone; anti-anxiety agents, such as sodium pentobarbital, chlorpromazine, and molindone; antidepressives, such as imipramine hydrochloride; stimulants, such as methyl phenadate and nikethamide; hallucinogens; analgesics, such as numorphan, meperidine, and morphine; and anorexigenic agents.

Other classes are pharmacodynamic agents, e.g., antihypertensive agents as reserpine, and chlorisondamine chloride, and antianginal agents, such as papaverine, and drugs for the therapy of pulmonary disorders, such as theophylline ethylenediamine salt and epinephrine. Additional classes are chemotherapeutic agents, e.g., antiviral; antiparasitic, such as emetine hydrochloride and stibophen; antifungal agents, such as cycloheximide; and antineoplastic agents, such as triethylene thiophosphoramide; agents affecting metabolic diseases and endocrine functions, e.g., prostaglandins; athersclerosins, such as heparin; steroids and biologically related compounds; polypeptides, such as bacitracin, polymyxin B sulfate, and sodium colistimethate; natural and synthetic hormones, such as estradiol dipropionate, progesterone, and hydroxy progesterone caproate; steroid and nonsteroidal antiinflammatory agents, such as gold sodium thiomalate and hydrocortisone sodium succinate; and agents affecting thrombosis, such as crystalline trypsin; vitamins, such as vitamin B_{12}; anti-epilepsy agents, such as phenobarbital; and the like. It should be understood that the specific drugs mentioned by name are illustrative and not limitative.

Endocrine agents comprise a particularly useful class of compounds in this invention and can be defined either